# Safety and Efficacy of Efruxifermin in Combination With a GLP-1 Receptor Agonist (GLP-1RA) in Patients with NASH/MASH and T2D: a Randomized, Placebo-controlled Study (Cohort D)

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## BACKGROUND

**Background:** Many patients with nonalcoholic steatohepatitis (NASH; metabolic dysfunction-associated steatohepatitis, MASH) have type 2 diabetes (T2D), which is increasingly treated with glucagon-like peptide-1 receptor agonists (GLP-1RA). There are no approved treatments for MASH. Efruxifermin (EFX) is an Fc–FGF21 analog that reduced liver fat content, improved liver histology, reduced markers of liver injury and fibrosis, and improved glucose and lipid metabolism in patients with MASH, with or without T2D. [1,2] The aim of this study (Cohort D) was to determine if EFX added to an existing stable dose of a GLP-1RA is tolerated in patients with MASH and T2D, and if there is potential for greater clinical efficacy.

## STUDY DESIGN AND BASELINE DEMOGRAPHICS

**Figure 1. Cohort D Study Design**


Patients (n=32) with MASH, fibrosis stages 1–3 (F1–F3), and T2D on stable GLP-1RA therapy (at least 90 days before screening, ~68% for more than 1 yr) were randomized 2:1 to receive once-weekly (QW) EFX (50 mg) or placebo for 12 weeks. The primary objective was to evaluate the safety and tolerability of EFX combined with a GLP-1RA. Secondary objectives were to determine effects on liver fat, markers of liver injury and fibrosis, markers of glucose and lipid metabolism, and body weight.

**Table 1. Baseline Demographics**

| Parameter (Mean, unless noted) | GLP-1RA + Placebo (N=10) | GLP-1RA + EFX 50 mg (N=21) |
|---|---|---|
| Mean age (years) | 55 | 59 |
| Sex (% female) | 90 | 43 |
| Race (% white) | 70 | 85.7 |
| Ethnicity (% Hispanic or Latino) | 0 | 28.6 |
| Weight (kg) | 96 | 101 |
| BMI (kg/m$^2$) | 35.4 | 35.0 |
| Fibrosis stage (% F1 / F2 / F3) | 40 / 10 / 50 | 38 / 33 / 29 |
| Hepatic fat fraction by MRI-PDFF (%) | 15.2 | 11.3 |
| Pro-C3 (µg/L) | 82 | 86 |
| ELF Score | 9.6 | 9.2 |
| Liver stiffness by VCTE (FibroScan) (kPa) | 12 | 10 |
| ALT (U/L) | 31 | 35 |
| AST (U/L) | 24 | 26 |
| HbA1c (%) | 6.5 | 7.0 |
| Triglycerides (mg/dL) | 171 | 163 |
| HDL-cholesterol (mg/dL) | 50 | 42 |
| Non–HDL-cholesterol (mg/dL) | 131 | 105 |
| LDL-cholesterol (mg/dL) | 98 | 73 |
| Statin use (%) | 50 | 81 |
| **GLP-1 Use** | | |
| Semaglutide (median dose: 1mg QW) | 60% | 43% |
| Dulaglutide (median dose 3mg QW) | 30% | 52% |
| Liraglutide (median dose 1.5mg once daily) | 10% | 5% |
| **Other Diabetes Medications** | | |
| Metformin | 70% | 76% |
| Insulin | 20% | 38% |
| SGLT2 inhibitor | 20% | 33% |
| Sulfonyl urea | 20% | 24% |
| DPP-IV Inhibitor | 0% | 10% |

Notes: With 1 exception, all patients remained on baseline GLP-1 therapy through Week 12. Due to unavailability of semaglutide, 1patient switched to tirzepatide after the Week-10 visit. Pro-C3 was analyzed on the ELISA Generation 2 platform.

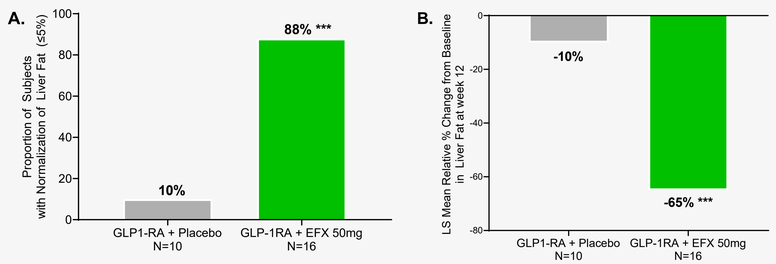
## RESULTS

**Table 2. Frequent Drug-related Adverse Events (Safety Set)**

| Treatment-Emergent Adverse Event (TEAE) Overview | GLP-1RA + Placebo (N=10) | GLP-1RA + EFX 50 mg (N=21) | All Subjects (N=31) |
|---|---|---|---|
| TEAE leading to death | 0 (0%) | 0 (0%) | 0 (0%) |
| Drug-related serious adverse event (SAE) | 0 (0%) | 0 (0%) | 0 (0%) |
| Drug-related TEAE leading to discontinuation | 0 (0%) | 1 (5%) | 1 (5%) |
| **Most Frequent (≥15%) Drug-related TEAEs** | | | |
| Diarrhea | 3 (30%) | 4 (19%) | 7 (23%) |
| Nausea | 1 (10%) | 7 (33%) | 8 (26%) |
| Increased appetite | 0 (0%) | 5 (24%) | 5 (16%) |
| Decreased appetite | 2 (20%) | 3 (14%) | 5 (16%) |

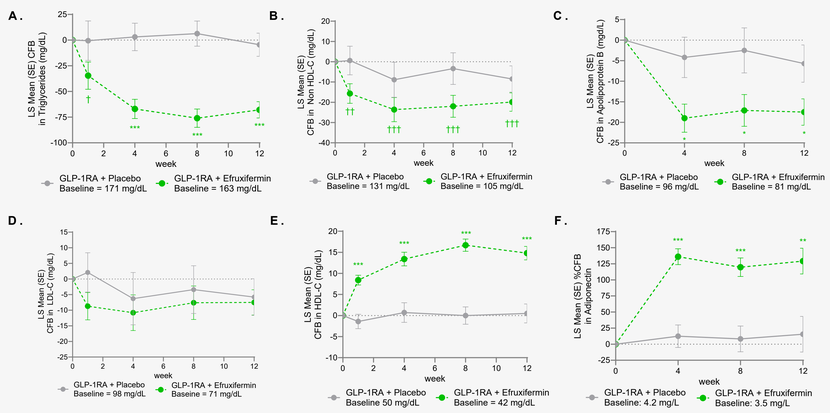
- The most frequent drug-related AEs were mild or moderate diarrhea, nausea, or increased appetite.
- There were 2 serious adverse events; neither were deemed drug related
- One patient discontinued due to a drug-related adverse event of Grade 2 nausea

**Figure 2. Effects of EFX Added to GLP-1 Receptor Agonists on Liver Fat After 12 Weeks (MRI-PDFF Analysis Set )**




**A.** Proportion of subjects that normalized liver fat to ≤5% by week 12 ***$P$<.001 vs placebo (Cochran-Mantel-Haenszel test) **B.** Relative change in liver fat at week 12. ***$P$<.001 vs placebo (ANCOVA)

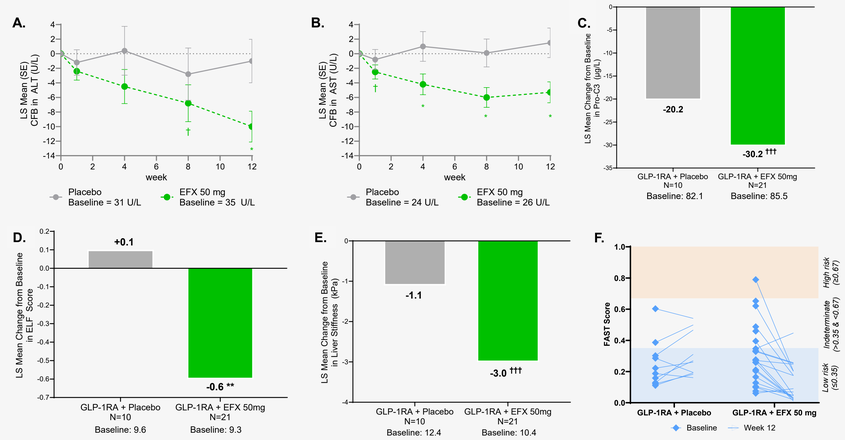
**Figure 3. EFX Added to a GLP-1RA Improved Lipoproteins and Adiponectin Over 12 Weeks (Full Analysis Set)**




## REFERENCES

1. Harrison SA, et al. (2021) *Nat Med* 27:1262-71
2. Harrison SA, et al. (epub Oct 03, 2023) *Lancet Gastro Hepatol.* DOI:10.1016/S2468-1253(23)00272-8

**Figure 4. EFX Added to a GLP-1RA Improved Non-invasive Markers of Liver Injury and Fibrosis Over 12 Weeks (Full Analysis Set)**




*P<.05, **P<.01 vs placebo; †P<.05, ††P<.01, †††P<.001 vs baseline (MMRM)

**Table 3. Categorical Changes in FAST Score After 12 weeks**

| Proportion of subjects with change in FAST category, n (%) | GLP-1RA + Placebo (N=10) | GLP-1RA + EFX 50 mg (N=19) |
|---|---|---|
| Improvement | 0 (0%) | 4 (21%) |
| No change | 9 (90%) | 14 (74%) |
| Worsening | 1 (10%) | 1 (5%) |

**Table 4. Changes in Markers of Glucose Metabolism From Baseline to Week 12**

| Least Squares Mean Changes From Baseline | GLP-1RA + Placebo | GLP-1RA + EFX 50 mg |
|---|---|---|
| HbA1c (%, absolute) | –0.2 | –0.5 ††† |
| Insulin (%) | –13 | –26 |
| C-peptide (%) | –3.5 | –22 † |
| Adiponectin (%) | +16 | +129 *** |

*** $P$<.001 vs placebo; † $P$<.05, ††† $P$<.001 vs baseline

**Weight Loss**

Patients receiving EFX while on GLP-1RA tended to lose more body weight (mean, –1.2 kg) than those receiving placebo while on GLP-1RA (mean, –0.8 kg).

**Table 5. Changes in Liver Histology with EFX Treatment in Patients With vs Without Background GLP-1RA Use in HARMONY Phase 2b Study (24 weeks, Patients with F2-F3)**

| | GLP-1RA Use | Placebo | EFX 28 mg | EFX 50 mg |
|---|---|---|---|---|
| Proportion of subjects with **≥1 stage improvement in fibrosis stage and No Worsening in MASH**, n / N (%) | Yes | 0 / 7 (0%) | 1 / 4 (25%) | 1 / 4 (25%) |
| | No | 8 / 34 (24%) | 14 / 34 (41%) | 13 / 30 (43%) |
| Proportion of subjects with **Resolution of NASH and ≥1 stage improvement** in fibrosis stage n / N (%) | Yes | 0 / 7 (0%) | 1 / 4 (25%) | 1 / 4 (25%) |
| | No | 2 / 34 (6%) | 10 / 34 (29%) | 13 / 30 (43%) |

## CONCLUSIONS

- **The tolerability of combined EFX and GLP-1RA appears comparable to that of GLP-1RA alone.**
- **EFX provided benefits over GLP-1RA alone, normalizing liver fat in most patients and further reducing markers of liver injury and fibrosis, while improving overall metabolic health through its action as an insulin sensitizer.**
- **The combination offers potential to accelerate improvements in histopathology among the many patients with MASH and T2D.**

## ACKNOWLEDGMENTS

The authors wish to thank the patients, their families, and study investigators. This study and all analyses were funded by Akero Therapeutics.

## CONTACT

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